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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,019	09/21/2001	Chikara Aizawa	SHIM1120	9316

28213 7590 09/19/2008

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EXAMINER	
LE, EMILY M	
ART UNIT	**PAPER NUMBER**
1648	
MAIL DATE	**DELIVERY MODE**
09/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/830,019	AIZAWA ET AL.	
	Examiner	Art Unit	
	EMILY LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on August 31, 2007

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7 and 17-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 7 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 17-21 are added. Claims 4-6 and 8-15 are cancelled. Claim 1-3, 7 and 17-21 are pending and under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3, 7, 16-18 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giuliani et al.,[1] in view of Esposito et al.[2]

The claims are directed to a method of making a composition comprising a) purifying a natural toxin selected form the group consisting of cholera toxin, pertussis toxin, heat-labile toxin of pathogenic E.coli, Staphylococcus alpha and beta toxins, and thermostable hemolytic toxin of Vibrio parahaemolyticus or a mutant toxin therefore to 95% or more purity; and attenuating the purified natural or mutant toxin by incubation in the presence of formalin at a temperature of 5° C to 40° C, wherein the purified and attenuated toxin has i) a residual toxic activity of less than 1/2000 that of the natural toxin, and an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin, and retains serine residues, glutamic acid residues, and

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[1] Giuliani et al. Mucosal Adjuvanticity and Immunogenicity of LTR72, a Novel Mutant of Escherichia coli Heat-labile Enterotoxin with Partial Knockout of ADP-ribosyltransferase Activity. J. Exp. Med. April 06, 1998, Vol. 187, NO. 7, 1123-1132.

lysine residues of the natural toxin in its amino acid sequence, except that a formalin molecule is bound to the lysine residue of the attenuated toxin. Claim 18, which depends on claim 17, requires the purified and attenuated toxin to be a mutant, wherein one or more amino acid residues are substituted, inserted, deleted or added, and having adjuvant activity, while the existing serine, glutamic acid and lysine residues are retained. Claim 20, which depends on claim 17, requires the residual toxic activity be less than 1/10000 of that of the natural toxin. Claim 21, which depends on claim 17, requires that the temperature does not exceed 40 °C. Claims 1-2, 7 and 16 are directed to the composition obtained by the method of claims 17-18 and 20-21, respectively.

Giuliani et al. teaches LTR72, a composition comprising a) purifying mutant heat-labile toxin of pathogenic E.coli toxin, wherein the purified and attenuated toxin has i) a residual toxic activity of less than 100,000 fold less toxic than that of the natural toxin. Giuliani et al. et al. teaches that the composition has adjuvant activity, thus, has an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin. Giuliani et al. et al. did not conduct site-mutagenesis on any serine, glutamic acid or lysine residues that is present in the amino acid sequence of the natural toxin. Hence, LTR72 retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence. LTR72 contains a substitution of Ala ==> Arg. Thus, LTR72 is a mutant, where one or more amino acid residues are substituted, inserted, deleted or added, and having adjuvant activity, while the existing serine, glutamic acid and lysine residues are retained.

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[2] Esposito et al. Effect of Formalin treatment on electrophoretic mobility of cholera toxin. Infection and Immunity, July 1970, Vol. 2, No. 1, p. 120-122.

Giuliani et al. did not also attenuate LTR72, which is already attenuated by substation of residue 72 from Ala ==> Arg and purified, in the presence of formalin at a temperature of 5° C to 40° C.

However, Giuliani et al. notes that LTR72, while having greatly reduced toxicity, still has a low residual level of toxicity. Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to further attenuate LTR72. At the time the invention was made, Esposito et al. teaches the detoxification of toxins using formalin at a temperature of 35°, which is between 5 °C and 40° C. Thus, it would have been prima facie obvious for one of ordinary skill in the art to combine the teachings of Esposito et al. with the teachings of Giuliani et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to render LTR72, an adjuvant, non toxic for pharmaceutical use. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because use of formalin around room temperature to detoxify toxins is well known in the art.

Additionally, while it is noted that Giuliani et al. purified the mutant toxin, it is not readily apparent if the purity is 95% or above. However, because Giuliani et al. does suggest the use of LTR72 as an adjuvant in pharmaceutical settings, it would have been prima facie obvious for one of ordinary skill in the art to purify LTR72 to a purity of 95% or above. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do to remove contaminants from the adjuvant to facilitate its use in a pharmaceutical setting. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the

determination of a workable range, including purity level, is routinely practiced in the art.

As previously noted, MPEP § 2144.05 [R3] [II] states: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Regarding the recitation, "formalin molecule is bound to lysine residues", it should be noted that this occurs as a consequence of the formalin treatment, as Applicant discloses in the specification. In the instant case, LTR72 has lysine residues, and the treatment of formalin would necessary render the formalin molecule bound to lysine residues. Thus, while neither the references address this, it is inherently provided by the treatment of formalin. It should be noted that the prior art does not need to appreciate this property to render the claimed invention obvious.

4. Claims 1-3, 7, 16-17 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esposito et al.

The claims are directed to a method of making a composition comprising a) purifying a natural toxin selected form the group consisting of cholera toxin, pertussis toxin, heat-labile toxin of pathogenic E.coli, Staphylococcus alpha and beta toxins, and thermostable hemolytic toxin of Vibrio parahaemolyticus or a mutant toxin therefore to 95% or more purity; and attenuating the purified natural or mutant toxin by incubation in the presence of formalin at a temperature of 5° C to 40° C, wherein the purified and attenuated toxin has i) a residual toxic activity of less than 1/2000 that of the natural toxin, and an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin, and retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence, except that a formalin molecule is bound to the lysine residue of the attenuated toxin. Claim 19, which depends on claim 17, requires the purified and attenuated toxin retain the same amino acid sequence as the natural toxin. Claim 20, which depends on claim 17, requires the residual toxic activity be less than 1/10000 of that of the natural toxin. Claim 21, which

depends on claim 17, requires that the temperature does not exceed 40 °C. Claims 1-3, 7 and 16 are directed to the composition obtained by the method of claims 17 and 19-21, respectively.

Esposito et al. teaches a composition comprising attenuated cholera toxin. Esposito et al. attenuated the toxin by incubation in the presence of formalin at a temperature of 35° C, which is between 5° C to 40° C. Esposito et al. does not teach modification of the amino acid sequence of the toxin, therefore, the attenuated toxin has the same amino acid sequence as the natural toxin, and retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence. Esposito et al. teaches that the toxin was detoxified.

Esposito et al. did not purify the toxin to 95% or more purity. However, Esposito et al. does suggest conducting future studies using purified form of the toxin. Therefore, it would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made to purify the toxin to purity of 95% or above. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do to remove contaminants from the toxin to facilitate its use in a pharmaceutical setting. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the determination of a workable range, including purity level, is routinely practiced in the art.

As previously noted, MPEP § 2144.05 [R3] [II] states: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Additionally, while Esposito et al. discloses that the toxin was detoxified, it was not readily apparent if the level of detoxification was less than 1/2000 and 1/10000. However, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to fully detoxify the toxin. As demonstrated by Esposito et al., the level of detoxification increases with time. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to obtain a

minimally toxic or toxic free product. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the determination of a workable range, including level of detoxification, is routinely practiced in the art.

Regarding the recitation, “formalin molecule is bound to lysine residues”, it should be noted that this occurs as a consequence of the formalin treatment, as Applicant discloses in the specification. In the instant case, LTR72 has lysine residues, and the treatment of formalin would necessary render the formalin molecule bound to lysine residues. Thus, while neither the references address this, it is inherently provided by the treatment of formalin. It should be noted that the prior art does not need to appreciate this property to render the claimed invention obvious.

Regarding the recitation, “an activity of enhancing production of an antibody specific to an antigen other than the attenuated toxin", it is noted that Esposito et al. does not appreciate this property. However, it is found that this property is inherent of the composition itself. As provided in MPEP 2112, the prior art does not need to appreciate this property to render the claimed invention obvious. The same section also notes that the discovery of an unrecognized or unappreciated property of a known composition does not render the composition patentable. In the instant case, the claimed composition is the same as the composition rendered obvious by Esposito et al., therefore, it would necessarily have adjuvant properties.

Conclusion

5. No claim is allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Le/
Primary Examiner, Art Unit 1648

/E. L./